IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Keith V. Wood et al.	Examiner: Rebecca E. Prouty
Serial No.:	09/645,706	Group Art Unit: 1652
Filed:	August 24, 2000	Docket No.: 341.005US1
Title:	SYNTHETIC NUCLEIC ACID MOLECULE COMPOSITIONS AND METHODS OF PREPARATION	

REPLY BRIEF UNDER 37 C.F.R. § 41.41

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Sir:

This Reply Brief is filed in response to the Examiner's Answer (hereinafter, the "Answer"), mailed December 12, 2007, and supplements the Appeal Brief filed by Appellant on August 23, 2007.

STATUS OF THE CLAIMS

The present application was filed on August 24, 2000 with 66 claims.

Claims 1, 45, 47, and 63 were amended, claims 10, 13, 16-17, 19, 22-23, 40, 46, 48-59, and 65-66 were canceled, and claims 67-68 were added in the Amendment filed on August 11, 2003. Claims 1-2, 14-15, 47, 61-63, and 67-68 were amended, claims 7-8 were canceled, and claims 69-73 were added in the Amendment filed on April 6, 2004. Claims 1 and 67 were amended and claims 74-80 were added in the Amendment filed on June 4, 2004.

Claims 1, 3-6, 9, 11-12, 15, 18, 20-21, 24-37, 42-43, 45, 47, 60, 67, 69-71, 74, 76-78, and 80 were amended, claims 2, 14, 61-63, 68, 72-73, 75, and 79 were canceled, claim 64 had been withdrawn, and claims 81-82 were added in the Amendment filed on December 13, 2004. Claims 1, 47, 67, 74, and 78 were amended and claims 83-94 were added in the Amendment filed on September 22, 2005. Claims 1, 18, 44, 47, 67, 71, 74, 78, 81-85, 90, and 92-93 were amended, claim 89 was canceled, and claims 95-96 were added in the Amendment filed on June 19, 2006 and claims 18, 47, 83, 90, and 95-96 were amended in the Amendment filed on February 12, 2007.

Claims 1, 3-6, 9, 11-12, 15, 18, 20-21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-88, and 90-96 are pending and are the subject of this Appeal.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The 35 U.S.C. § 112, Second Paragraph, Rejections to be Reviewed

Whether claims 1, 3-6, 9, 11-12, 15, 20-21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-82, 85-88, and 90-96 are unpatentable under 35 U.S.C. § 112, second paragraph.

Whether claim 90, which depends on claim 1, is unpatentable under 35 U.S.C. § 112, second paragraph.

The 35 U.S.C. § 112, First Paragraph, "Enablement" Rejection to be Reviewed

Whether claims 1, 3-6, 9, 11-12, 15, 20-21, 24-33, 35-39, 41-45, 60, 67, 69-70, 81, 86, 88, and 90-95 lack enablement under 35 U.S.C. § 112, first paragraph.

The 35 U.S.C. § 103(a) Rejections to be Reviewed

Whether claims 1, 3-6, 9, 11-12, 15, 20-21, 24-39, 41-45, 60, 67, 69-70, 81, 86, and 90-95 are unpatentable under 35 U.S.C. § 103(a) over Sherf et al. (U.S. Patent No. 5,670,356) in view of Zolotukhin et al. (U.S. Patent No. 5,874,304), Donnelly et al. (WO 97/47358), Pan et al. (Nucl. Acids Res., 27:1094 (1999)), Cornelissen et al. (U.S. Patent No. 5,952,547), and Hey et al. (U.S. Patent No. 6,169,232).

Whether claim 95, which depends on claim 67, is unpatentable under 35 U.S.C. § 103(a) in view of Sherf et al., Zolotukhin et al., Donnelly et al., Pan et al., Cornelissen et al., and Hey et al.

Whether claims 18, 47, 71, 74, 76-78, 80, 82-85, 87-88, and 96 are unpatentable under 35 U.S.C. § 103(a) over Sherf et al., in view of Zolotukhin et al., Donnelly et al., Pan et al., Cornelissen et al., and Hey et al., and further in view of Wood et al. (WO 99/14336).

Whether claim 96, which depends on claim 74, is unpatentable under 35 U.S.C. § 103(a) over Sherf et al., Zolotukhin et al., Donnelly et al., Pan et al. Cornelissen et al., Hey et al., and further in view of Wood et al.

REPLY

In the Answer, the Examiner indicated that the following sections of the Appeal Brief filed on August 23, 2007 included errors: "Status of the Claims" and "Grounds of Rejection to be Reviewed on Appeal".

A revised "Status of the Claims" section and a revised "Grounds of Rejection to be Reviewed on Appeal" section (which reflects the withdrawal of the rejection of certain claims as noted on page 4 of the Answer) is enclosed herewith.

At pages 4-5 in the Answer, the Examiner asserts that Appellant's Appeal Brief has failed to comply with the subheading requirement of 37 C.F.R. § 41.37(c)(1)(vii) for claims that are argued separately (i.e., claims 90, 95 and 96). 37 C.F.R. § 41.37(c)(1)(vii) states that "any claim argued separately should be placed under a separate subheading" (emphasis added). In contrast, 37 C.F.R. § 41.37(c)(1)(vii) also states that "each ground of rejection must be treated under a separate heading" (emphasis added). As Appellant has separately argued the patentability of claims 90, 95 and 96 (see pages 20, 42-43 and 47 of the Appeal Brief), and there is no requirement that subheadings must be employed for claims argued separately, Appellant's Appeal Brief is in compliance with 37 C.F.R. § 41.37(c)(1)(vii).

The Answer has raised several points in response to the arguments presented in the Appeal Brief. The following section of the Reply Brief addresses those points and supplements the arguments presented in the Appeal Brief filed on August 23, 2007, which demonstrates that contrary to the Examiner's contentions, the present application fully meets the requirements of 35 U.S.C. § 112(1), § 112(2) and § 103.

The 35 U.S.C. § 112, Second Paragraph, Rejection

In the Answer, the Examiner asserts that many variants of the consensus poly(A) addition signal can also act as poly(A) addition signals and it is unknown which are included in the scope of that term (page 8 of the Answer). The Examiner provided no documentation to support that assertion and is respectfully requested to make that documentation of record in the present appeal.

Assuming, for the sake of argument, that there are many variants of the consensus poly(A) addition signal that can act as poly(A) addition signals, it is Appellant's position that since those sequences are known ("many variants of the consensus poly(A) addition signal can also act as poly(A) addition signals") and have a definite property ("act as poly(A) addition signals") that is recognizable by one of skill in the art (either by inspection of a nucleic acid sequence for a sequence that is structurally related to a consensus poly(A) addition sequence or by testing whether that sequence leads to polyadenylation of an approximately linked sequence), the phrase "poly(A) addition sites" is definite within the meaning of 35 U.S.C. § 112, second paragraph.

At pages 8 and 20 in the Answer, the Examiner contends that the function of many of the recited groups of transcription regulatory sequences (TRSs) is often dependent upon the context in which they are found (e.g., surrounding sequences).

Even if, assuming, for the sake of argument, nucleotide sequences surrounding a TRS may influence the efficiency of binding of a transcription factor to a transcription factor binding sequence (TFBS), splicing by splice sites, poly(A) addition by poly(A) addition sites, or transcription initiation in prokaryotes from 5' noncoding regulatory sequences, the identification of TRSs does not require that a particular nucleic acid sequence be tested for its function. Rather, the presence or absence of one or more TRSs in a selected nucleic acid sequence may be ascertained by inspection of the primary sequence. That is because TFBSs, intron splice sites, poly(A) addition sites and prokaryotic 5' noncoding regulatory sequences are sequences recognized by the art, as discussed in the Appeal Brief filed on August 23, 2007.

The Examiner asserts that the calculation of a reduced number of TFBSs in a nucleotide sequence is impossible in the absence of a specific list of sequences to be identified (page 7 and the overlapping sentence at pages 23-24 and the subsequent sentence on page 24 in the Answer), and that the same nucleotide sequence may be within the scope of the claims if a new member of any of the recited groups is searched but not be within the scope of the claims if that new member is omitted from the search (page 22 in the Answer).

The Board is requested to consider that it is not the actual number of members on any "list" that is needed for the calculation, it is a comparison of two sequences, i.e., a comparison of the nucleotide sequences of a wild type or parent reporter protein encoding nucleic acid sequence and of the recited second synthetic nucleic acid molecule, and a comparison of the nucleotide sequences of the recited second synthetic nucleic acid molecule and of the recited first synthetic nucleic acid molecule. Mammalian high usage codons that replace codons in the wild type or parent reporter protein nucleic acid sequence are selected to result in a reduced number of at least a combination of different mammalian TFBSs in the second synthetic nucleic acid molecule and codons in the second synthetic nucleic acid molecule are replaced with mammalian codons to result in a reduced number of at least a combination of different mammalian TFBSs in the first synthetic nucleic acid molecule.

With regard to the alleged change in scope of the claims by "adding" a TFBS to be identified, while that TFBS may be present one or more times in a wild type or parent reporter protein encoding nucleic acid sequence, and so result in potential site(s) for codon replacement, many other TFBSs are still present one or more times in the wild type or parent reporter nucleic acid sequence, and so are also potential sites for codon replacement. In this regard, the Board is requested to recall that prior to Appellant's effective filing date a large number of TFBSs were already known (see, e.g., Faisst and Meyer, Nucl. Acids Res., 20:3 (1992), which provided a compilation of about 150 vertebrate transcription factors and their binding sequences; of record) and that although Sherf et al. (U.S. Patent No. 5,670,356, a reference cited against the claims under 35 U.S.C. § 103(a)) removed a small number of TFBSs from a wild type firefly luciferase sequence resulting in *luc+*, the *luc+* gene still contained over 150 potential mammalian transcription factor binding sites (see the Rule 132 Declaration filed on June 19, 2006; of record).

Thus, although there may be new members added to any of the groups of TRSs over time, the claims in the present application provide that the synthetic reporter protein encoding nucleic acid molecules have a reduced number of a combination of different mammalian TFBSs as a result of codon replacement of a wild type or parent reporter protein encoding nucleic acid sequence with mammalian codons.

Therefore, Appellant's synthetic nucleic acid molecule with a reduction in a combination of different mammalian TFBSs is definite.

Accordingly, the claims satisfy the requirements of 35 U.S.C. § 112, second paragraph.

The 35 U.S.C. § 112, First Paragraph, "Enablement" Rejection

The Examiner asserts that the specification does not establish a) regions in the protein encoded by the synthetic nucleic acid molecules which may be modified without effecting activity, b) the general tolerance of any protein to modification and the extent of that tolerance, c) a rational and predictable scheme for modifying residues in a protein with an expectation of obtaining the desired activity, and d) which of the infinite possible choices for amino acid substitutions is likely to be successful (pages 12-13 of the Answer).

The claims are not directed to any protein, but rather to particular reporter proteins that are well-known and well-characterized (claims 1, 67 and 92). That is, wild type nucleic acid sequences for chloramphenicol acetyltransferase, *Renilla* luciferase, beetle luciferase, beta-lactamase, beta-glucuronidase and beta-galactosidase were known to the art prior to Appellant's filing (Wood et al., Science, 244:700 (1989), Ye et al., Biochem. Biophy. Acta, 1339:39 (1997), Murray et al., J. Mol. Biol., 254:993 (1995), Zhang et al., Proc. Natl. Acad. Sci. USA, 94:4504 (1997), Lorenz et al., Proc. Natl. Acad. Sci. USA, 88:4438 (1991), Sirot et al., Antimicr. Agents Chemo., 41:1322 (1997); Lorenz et al., Proc. Natl. Acad. Sci. USA, 88:4438 (1991), Murray et al., J. Mol. Biol., 254:993 (1995); all of record). Moreover, reporter proteins with substitutions and reporter activity, such as variants of chloramphenicol transferase, beta-lactamase, beta-glucuronidase, and beetle luciferase were also known prior to Appellant's filing (see, e.g.,

Stapleton et al., Antimicrob. Agents Chemother., 43:1881 (1999), Bouthors et al., Protein Eng., 12:313 (1999), Voladri et al., J. Bacteriol., 178:7248 (1996), Murray et al., J. Mol. Biol., 254:993 (1995), WO 99/14336, and Matsumura et al., Nat. Biotechnol., 17:696 (1999); all of record).

Given that the specification is enabling for a variant of a parent DNA molecule encoding a reporter polypeptide that is identical to a reporter polypeptide encoded by the parent DNA and for a variant of a parent DNA molecule encoding a luciferase having 90% identity to the polypeptide encoded by SEQ ID NO:2, which variants have more than 25% of the codons altered and have a reduced number of TFBSs, introns splice sites, poly(A) addition sites and prokaryotic 5' noncoding regulatory sequences relative to a mammalian codon optimized variant of the parent nucleic acid (see pages 9-10 of the Answer), in view of well-known and well-characterized sequences for beta-galactosidase, chloramphenicol acetyltransferase, beta-lactamase, beta-glucuronidase, and luciferase and the skill of the art worker (it is "high"), it is logical to conclude that claims directed to synthetic nucleic acid molecules encoding chloramphenicol acetyltransferase, *Renilla* luciferase, beetle luciferase, beta-lactamase, beta-glucuronidase or beta-galactosidase with at least 90% amino acid sequence identity to a wild type chloramphenicol acetyltransferase, *Renilla* luciferase, beetle luciferase, beta-lactamase, beta-glucuronidase or beta-galactosidase, are enabled.

The Examiner concedes that firefly and click beetle luciferases have been extensively modified and that the art provides a substantial amount of guidance for making active variants thereof (overlapping sentence at pages 27-28 in the Answer). Based on that and the acknowledgment by the Examiner that the specification is enabling for a variant of a parent DNA molecule encoding a luciferase having 90% identity to the polypeptide encoding by SEQ ID NO:2 (a beetle luciferase) and having more that 25% of the codons altered and having a reduced number of TFBSs, introns splice sites, poly(A) addition sites and prokaryotic 5' noncoding regulatory sequences than a mammalian codon optimized variant of SEQ ID NO:2 (pages 9-10 of the Answer), it is unclear to Appellant why the specification does not enable the synthetic nucleic acid molecule recited in claim 67, as that synthetic molecule encodes a luciferase with at least 90% identity to a wild type beetle luciferase.

Further, even if, assuming for the sake of argument, as of Appellant's effective filing date, a complete characterization of which residues in a particular reporter protein could be

modified without effecting reporter activity was not available, it is Appellant's position that as of that date it was well within the skill of the art worker to prepare reporter proteins where up to 10% of selected residues were substituted (e.g., positions for substitutions were selected based on crystal data or predictive software) and screen those for variants with reporter activity, with a reasonable expectation of obtaining such variant reporter proteins. In this regard, in the Office Action dated January 6, 2004, the Examiner commented that "a skilled artisan could easily determine if any variant retained the function of the parent nucleic acid" (page 7 of that Office Action). It is also Appellant's position that as of Appellant's effective filing date it was well within the skill of the art worker to screen libraries encoding variant reporter protein sequences, e.g., libraries expressing sequences that had been subjected to random mutagenesis and recombination, to identify members of the library with reporter activity and likely encoding a protein with numerous substitutions. Evidence that screening of populations of molecules to identify proteins with specific properties was routine in the art, and so does not constitute undue experimentation, was provided with the Appeal Brief filed on August 23, 2007.

Therefore, based on information available to the art worker on residues that may be modified in a reporter protein, one of skill in the art could without undue experimentation prepare and identify variants of chloramphenicol acetyltransferase, *Renilla* luciferase, beetle luciferase, beta-lactamase, beta-glucuronidase or beta-galactosidase with at least 90% amino acid sequence identity to, and the reporter activity of, a wild type counterpart, particularly due to the ease of detecting reporter activity.

The Examiner asserts that there is nothing in In re Wands and Hybritech to suggest that a large amount of the scope of those claims (the antibodies) could not be isolated by the screening methods disclosed in the art, in contrast to the art available screening methods in the present case (page 33 of the Answer). The Examiner also asserts that a skilled artisan would be well aware that as the number of modifications increases, the number of possible sequences increases exponentially, while the number of active sequences decreases exponentially (page 32 in the Answer), and that the instant claims would require screening of several billion or more to find active mutants (page 33 in the Answer).

The Examiner did not provide support for any of those assertions and so is requested to do so (see M.P.E.P. § 2164.04). Moreover, it cannot be reasonably contended that one of skill in the art would not design or screen libraries of synthetic nucleic acid molecules to identify synthetic sequences that may encode a variant reporter protein simply because that variant may be "rare", especially because reporter activity is readily detected.

In response to the citations provided in the Answer to show the diversity of luciferases (pages 28-30 of the Answer), the Board is urged to consider that none of these citations supports the proposition that modifying the amino acid sequence of a beetle luciferase or a *Renilla* luciferase to yield a variant luciferase with at least 90% amino acid sequence identity to the parent beetle or *Renilla* luciferase is wholly unpredictable. The Board is also requested to consider that the Examiner has acknowledged that the art provides a substantial amount of guidance for making active variants of firefly and click beetle luciferases.

Thus, the pending claims are in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The 35 U.S.C. § 103 Rejections

Reply to the Characterization of the References Cited Against the Claims

The Examiner alleges that Sherf et al. teach a modified firefly luciferase gene in which 14% of the codons were altered to optimize codon selection for human cells and eliminate restriction sites and sequences which encode TFBSs for mammalian transcription factors (page 14 of the Answer).

Sherf et al. disclose a synthetic firefly luciferase gene (*luc*$^+$) the sequence of which was altered primarily to remove the peroxisomal translocation sequence so as to yield a cytoplasmic form of the enzyme (abstract; column 2, lines 59-61). The sum of alterations disclosed in Sherf et al. (with up to 17 individual alterations that are unrelated to codon usage alterations) may alter post-translation steps (glycosylation), the translation product (i.e., lack of peroxisomal translocation sequence), RNA secondary structure (palindromes, and possibly RNA sequences

corresponding to restriction endonuclease sites), transcription (TFBS), or sequences unrelated to transcription or translation (restriction endonuclease sites).

Thus, Sherf et al. disclose limited alterations of specific sequences in a wild type firefly luciferase encoding nucleic acid molecule, where the alterations are intended to alter transcription, translation and other activities.

The Examiner notes that Zolotukhin et al. insert their codon altered GFP gene into a vector that has a Kozak consensus sequence 5' to the ATG (page 15 of the Answer).

Zolotukhin et al. disclose that codons were altered in order to address the poor translation efficiency of the *gfp* nucleic acid sequence in human cells (column 12, lines 49-51), as an alternative method to increase expression by, for example, insertion of an intron (column 43, lines 26-32) or the introduction of a Kozak sequence, the latter of which did not significantly change expression (column 43, lines 49-60).

The Examiner contends that Cornelissen et al. state that wholesale (nonselective) changes in codon usage can introduce cryptic regulatory signals in a gene, thereby causing problems in one or more of transcriptional control, RNA processing control, RNA transport control, mRNA degradation control, translational control and protein activity control, which in turn inhibits or interferes with transcription and/or translation (pages 35 and 52-53 in the Answer), and that that portion of Cornelissen et al. shows that the art did recognize that codon replacement can create additional TFBSs.

There is nothing in the cited portion of Cornelissen et al. that "explicitly" teaches that codon replacement may create unwanted TFBSs, as suggested by the Examiner at pages 38 and 56 in the Answer.

The Examiner also alleges that Hey et al. teach a plant sink protein gene with altered codons without an altered protein sequence (page 17 of the Answer) and that although Hey et al. discuss optimizing a gene for expression in plants instead of for expression in mammals, a skilled artisan would understand that the same basic strategy is used to optimize in either host with the only distinction being the use of a different preferred codon list (page 42 in the Answer).

Hey et al. clearly discloses altering codons in storage proteins to yield sink protein nucleic acid sequences that have Trp codons for Phe codons (amino acid substitutions which result in an altered protein sequence).

The Board is requested to contemplate that Hey et al. do not disclose or suggest "the same basic strategy" for optimizing a gene as recited in the pending claims, as the mammalian codons in Appellant's synthetic nucleic acid molecules are selected to reduce the number of mammalian TFBSs.

The Examiner asserts that Wood et al. clearly disclose nucleic acids encoding wild type Luc*Ppl*YG, a luciferase having 97% identity to the protein encoded by SEQ ID NO:2 (page 19 in the Answer).

While Appellant's synthetic nucleic acids may encode a luciferase with at least 90% amino acid sequence identity to a wild type luciferase, the nucleic acids disclosed in Wood et al. were selected to encode thermostable luciferases, and not selected to reduced the number of TRSs.

Reply to the Examiner's Assertions with Regard to the Combination of the Cited References

The Examiner alleges that Appellant's solution to the problem of gene optimization is whole sale changes in codon usage followed by additional changes to the codon optimized sequence to eliminate the unwanted sequences that were introduced during optimization, and that the mere teaching of a second solution to a problem does not teach away from the first solution (pages 36 and 52-53 of the Answer).

However, the teachings in the cited documents are not logically combinable: to achieve an "improved" gene you either modify a small number of the codons in a coding sequence or a large number of the codons in a coding sequence to eliminate specific types of sequences in specific ways. Moreover, Cornelissen et al. disclose that instead of modifying the codon usage, undesirable sequence elements are inactivated, preferably by introducing an intron (column 11, lines 31-35). Therefore, there is no clear guidance in the cited art leading to Appellant's claimed invention. The combining of select teachings in Sherf et al. (limited and targeted changes) and Cornelissen et al. (limited and targeted changes) with those in Zolotukhin et al., Pan et al.,

Donnelly et al., and Hey et al. (for the Examiner to support the rejection of some of the pending claims), and also in some instances the teachings in Wood et al. (for the Examiner to support the rejection of other claims), can only result from impermissible hindsight reconstruction, i.e., picking and choosing from select disclosures in each of those documents with knowledge of Appellant's invention.

The Examiner also asserts that the disclosures of Hey et al., Donnelly et al., and Pan et al. would have clearly led a skilled artisan to scan not only the wild type sequence for the unwanted transcription factor binding sites but also the codon optimized version thereof, and that although the art does not explicitly teach iterative removal of TFBSs from a codon altered gene, it does suggest it (page 39 of the Answer). The Examiner contends at page 46 of the Answer that while greater changes increase the chance that a detrimental sequence will be introduced, the art also teaches how to remedy this potential drawback by rechecking the optimized sequence to eliminate newly created undesired sequences. The Examiner further contends that while the removal of TFBSs might require more than a single nucleotide change to accomplish and might be more difficult than removing other sites, there is no reason to believe that a skilled artisan could not select alterations to the sequence which would eliminate these sites as well even if this required modifying more than one nucleotide of the sequence (page 47 of the Answer).

If, in fact, the more changes that are made to a sequence, the higher the chances are that a detrimental sequence will be introduced (pages 39 and 57 of the Answer), one of skill in the art would follow the teachings of Sherf et al. or Cornelissen et al. (limited and targeted changes) to address the same problem addressed by Zolotuhkin et al., Donnelly et al., Pan et al., and Hey et al. Thus, by introducing limited changes, one of skill in the art creates fewer potential detrimental sequences.

Since Sherf et al. (issued in 1997) report removing among other sequences TFBSs, it is unclear how the disclosures of Hey et al. (issued in 2001), Pan et al. (dated 1999), and Donnelly et al. (published in 1997), would have led one of skill in the art to iteratively remove TFBSs from a codon optimized sequence, as Pan et al. and Hey et al. post-date Sherf et al. by at least about 2 years, yet make no mention of the desirability of TFBS removal. Moreover, given the Examiner's proposition that the art would be led to alter all types of detrimental sequences (page

43 of the Answer), it is curious (and revealing) why each cited document does not disclose removing the sum of all the undesirable sequences disclosed in documents that pre-date it.

The Board is requested to consider that although Donnelly et al. and Pan et al. disclose rechecking a codon modified sequence for particular sequences, none of those sequences included TFBSs. Further, only a few TFBSs were removed from a wild type firefly luciferase sequence in Sherf et al., even though Sherf et al. disclose that the luciferase gene sequences were scanned using a database of consensus TFBSs, citing Faisst and Meyer, *supra* (column 8, lines 65-66 in Sherf et al.). Continuing, Sherf et al. disclose that "[m]any sites which could potentially interact with common factors were removed. In some cases…less common potential regulating sites were also removed" (column 9, lines 1-4). Nevertheless, the product of the disclosed improvements, *luc+*, had over 150 potential mammalian TFBSs (see the Wood Declaration, filed on June 19, 2006; of record).

Moreover, one of skill in the art would not reasonably expect that mammalian codon optimization would introduce mammalian TFBSs, particularly given the complexity of the sequence for many vertebrate TFBSs (see the table in Faisst and Meyer, *supra*).

The Examiner cites KSR International Co. v. Teleflex Inc. et al., 550 U.S. ____, 82 U.S.P.Q.2d 1385 (2007) (pages 47 and 60 of the Answer) to support the position that an invention that is "obvious-to-try" may be obvious as well.

First, the issue in KSR v. Teleflex was whether mounting a modular sensor on a fixed pivot point of a pedal was a design step within the grasp of a person of ordinary skill in the art, in view of two cited documents. The Court noted that following the principles underlying case law with regard to obviousness "may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for improvement". *Id.,* at 1396. The Court held that the claim at issue was obvious in view of the combination of the two cited documents.

In the present Appeal, claims directed to a first synthetic nucleic acid molecule encoding a particular reporter protein, wherein the codon composition of the first synthetic nucleic acid molecule is different from that of a corresponding wild type nucleic acid sequence and of a second synthetic nucleic acid molecule which encodes the reporter polypeptide, wherein the

codons that are different are mammalian codons selected to result in a reduced number of a combination of different mammalian TFBSs, are alleged to be obvious in view of a combination of six or seven documents. As discussed herein and in the Appeal Brief filed on August 23, 2007, the presently claimed subject matter does not involve the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art.

With regard to obvious-to-try, the Court in KSR v. Teleflex stated that where there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a combination that was obvious-to-try might show that the combination was obvious. *Id.*, at 1397 (emphasis added).

It is Appellant's position that the cited documents solved the problem of gene optimization. And even if, assuming for the sake of argument, there was a need to provide other types of optimized genes, the combination of the cited documents does not provide a finite number of predictable solutions to prepare an improved gene. In fact, the cited documents provide no single direction on how to "optimize" a gene.

While it is true that the claims are not limited to synthetic nucleic acid molecules in which only TRSs are eliminated (page 42 of the Answer), the claims affirmatively recite that the number of a combination of different mammalian TFBSs in the synthetic nucleic acid molecules is reduced as a result of selected codon replacement.

At pages 41 and 59 of the Answer, the Examiner contends that the claims do not recite replacement with other lower usage mammalian codons. Nevertheless, to allow for removal of a TRS from a sequence with high usage mammalian codons, at least one of those codons is replaced with a lower usage codon for the same amino acid, if the codon substitution is "silent" (i.e., does not result in an amino acid substitution). In this regard, please consider that the claims recite that codons that are different in the second synthetic nucleic acid molecule (relative to the wild type or parent nucleic acid) are those high usage mammalian codons which are selected to reduce the number of at least a combination of mammalian TFBSs and that the codons that are different in the first synthetic nucleic acid molecule (relative to the second synthetic nucleic acid molecule) are mammalian codons which are selected to reduce the number of at least a combination of mammalian TFBSs.

At pages 44 and 64 in the Answer, the Examiner asserts that claims 90, 95 and 96 do not further limit the base claim. The Board is requested to consider that the splice site sequences, poly(A) addition sequence, prokaryotic 5' noncoding regulatory sequences and the identified mammalian TFBSs in a database that includes TFBSs, mutant TFBSs and consensus TFBSs or TFBSs with partial ambiguity to those in the database in the synthetic nucleic acid molecules recited in claims 90, 95 and 96, limit the "intron splice sites", "poly(A) addition sites", "prokaryotic 5' noncoding regulatory sequences" and the mammalian TFBS that are reduced and are present in a database of TFBS in the synthetic nucleic acid molecules recited in claims 1, 67 and 74.

With regard to the rejection of claims 18, 47, 71, 74, 76, 78, 80, 82-85, 87-88 and 96, the Examiner did not provide support for the assertion that high stringency conditions allow for up to 5% of the total positions to be different (page 62 of the Answer), and so is requested to do so in the next Official Action (see M.P.E.P. § 2144.03).

In addition, the Board is requested to consider that the Examiner cannot reasonably support the position that SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:18, SEQ ID NO:297 and SEQ ID NO:301 are obvious in view of the cited documents, particularly given the nucleotide sequence divergence between those SEQ ID NOs. and a corresponding wild type or parent nucleotide sequence, which divergence is based on removal of TRSs. Therefore, sequences that hybridize thereto under specific conditions (claims 18, 47 and 78) are in compliance with 35 U.S.C. § 103.

Accordingly, a *prima facie* case of obviousness has not been made out for claims 1, 3-6, 9, 11-12, 15, 20, 21, 24-39, 41-45, 60, 67, 69-70, 81, 86, and 90-95 nor for claims 18, 47, 71, 74, 76-78, 80, 82-85, 87-88, and 96.

CONCLUSION

It is respectfully submitted that the specification and claims of the present application satisfy the requirements of 35 U.S.C. § 112, first and second paragraphs, and that the claims are not obvious over the cited art. Therefore, reversal of the rejections and allowance of the pending claims is respectfully requested.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 27 day of February, 2008.

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